PATENT
01961-P0209B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	Nicholas V. Perricone.
Application No. 10/750,390	Filing Date: Dec. 31, 2003
Title of Application:	Methods of Formulating Stablized Insulin Compositions
Confirmation No. 8977	Art Unit: 1616
Examiner	Ernst V. Arnold

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Reply Brief Under 37 CFR §41.41

Dear Sir:

Appellant submits this Reply Brief for the above-captioned application pursuant to 37 C.F.R. §41.41 as follows.

Appellant has fully set forth its arguments for patentability in its previously filed Appeal Brief, and therefore will not repeat its arguments herein.

Reply to Response to Argument

The Examiner argues, with respect to the rejection of claims 1-6, 8, and 11-16 under 35 U.S.C. §112, first paragraph, for failure to comply with the written description requirement, that Applicant's multilamellar liquid crystals could be liposomes; and that the Examiner believes that a carrier comprised of polar molecules must necessarily

itself be a polar structure. The Examiner refuses to believe the written specification "in the absence of evidence to the contrary." (Answer at 12).

A review of the prosecution history of this application will reveal the Applicant's repeated efforts to present claims directed at a method of formulation of a stable topical insulin product using a multilamellar liquid crystal, which is not a liposome, as the carrier; and the Examiner's reliance on liposome prior art as the basis for rejection; and the Examiner's insistence that the Applicant's claim language reads on liposome prior art, despite multiple amendments directed at clarifying the claims as using a multilamellar liquid crystal. Ultimately, the terms "non-liposome" and "non-polar" were inserted in the claims in the in the claim language to explicitly disclaim any liposome structures. In response, the Examiner entered the §112 rejections and has refused to believe that the claimed structure is possible. The Reply argues that "Applicant could be making vesicles of some type" (Reply at 12); and that the combination of polar molecules would clearly give rise to a "polar" carrier. Thus, despite the explicit language of the specification at ¶[0009] (Page 3, line 7) and ¶[0013] (Page 4), the Examiner does not believe the Applicant.

However, the issue posed by the written description requirement is whether the disclosure of the specification supports the claims presented. Here, clearly the specification supports the claims presented.

The fact that the Examiner does not believe the claimed invention can exist is a different question. The claimed invention is described in the specification.

The Examiner argues, with respect to the rejection of claims 1-6, 8, and 11-16 under 35 U.S.C. §112, second paragraph, that the claim language "non-polar carrier" is indefinite. (Answer at 13-14).

As previously discussed, the claim language in question is intended to define a liquid crystal structure that is not likely to form a liposomal structure. The term "non-polar" is incorporated in this definition to make clear that the carrier is a liquid crystal structure which is multilamellar but not likely to form a liposome. The term "non-polar" as used in the claim defines the carrier structure, not the phosphatidylcholine molecule.

The Examiner nevertheless asserts, without any supporting evidence, that the claims are indefinite because a phosphatidylcholine/polyglycol carrier must necessarily be a polar structure. The Examiner's position is essentially that the claimed subject matter is scientifically impossible and thus is indefinite. This is error.

> "Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

M.P.E.P. §2107.02. The Examiner has not come forward with any evidentiary support for the rejection. This does not give rise to a prima facie case of indefiniteness. See e.g., *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); M.P.E.P. §2107.02. In contrast, Applicant has relied on Esposito, *Lipid-Based*

Supramolecular Systems for Topical Application: A Preformulatory Study, AAPS PharmSci 2003; 5 (4) Article 30; see also, Hansen, U.S. Patent 5,955,502 at Col. 6, lines 33-60. In such circumstances, the rejection under 35 U.S.C. §112, second paragraph should be overruled.

The Examiner argues, with respect to the rejection of claims 1-6, 8, and 11-16 under 35 U.S.C. §103, that Amselem is not directed at liposomes. (Answer at 14). Yet, Amselem clearly defines "emulsomes", which are liposome-like structures which are fundamentally different from the loosely arranged multilamellar liquid crystal structure claimed in this application. The emulsome structures of Amselem have a solid phase lipid core and are surrounded by phospholipids. Hydrophobic drug loading in the internal solid lipid core permits parental delivery of hydrophobic drugs. The rejection based on Amselem relies on a structure which is not the same as the claimed structure. Even if claim 1 of Amselem discloses a phospholipid bilayer surrounding the internal solid core, the structure of the phospholipid bilayer in Amselem is not the claimed non-liposomal multilamellar liquid crystal phosphatidylcholine non-polar carrier of the present invention. Amselem's emulsomes have "the characteristics of both liposomes and emulsions". The structure of the phospholipid bilayer in Amselem is a liposome-like bead structure, not a "multilamellar liquid crystal structure", and accordingly, Amselem does not make the claims obvious. Amselem does not disclose or suggest the use of a non-liposomal multilamellar liquid crystal phosphatidylcholine non-polar carrier entrapping insulin for transdermal delivery of the insulin to dermal vasculature.

The description of saturated or unsaturated phospholipid components in Amselem does not make the claimed invention obvious.

The importance of the present invention is that it provides a method of formulating stable topical insulin compositions that are stable for much longer than insulin solutions stored at room temperature. This is a significant benefit to diabetic patients, particularly those located in geographic regions such as Africa or Asia where reliable refrigeration may not be available. There is no disclosure in Amselem or the other art of record of providing a room temperature stabilized insulin composition as described in the present claims and specification. Neither the disclosed invention nor its benefits are disclosed or suggested by the combination of references.

The presently claimed invention defines a specific method of formulating topical insulin that is directed at making a carrier in a multilamellar liquid crystal phase which is effective to formulate a stable topical insulin composition, thus avoiding the need for refrigeration of insulin, and providing a vehicle for distribution of insulin in remote areas where refrigeration is unavailable.

Furthermore, the Response To Argument does not respond to the Applicant's arguments about the patentability of the specific method steps presented in dependent claims 2-6, 8, and 11-16. The Response To Argument does not provide any basis for concluding that the use of the specifically claimed combination of phosphatidylcholine and polyglycols of two different molecular weights (200 and 400) would have been obvious, and for this additional reason, claims 2 and 3-6, and 8 are patentable over the

cited art. In the same way, The Response To Argument does not provide any basis for concluding that claims 5 and 16, which specify warming the phosphatidylcholine solution to 40°C and milling the warmed solution; and that siloxylated polyether and polydimethylsiloxane are combined to form a fluid which is added to the warmed solution; and that methyl paraben is added to the solution and milled until it dissolves; and that water warmed to 40°C is added slowly to said solution; then cooled to room temperature while sweeping it. Nor is any basis given for the use of lubricious silicone fluids and/or siloxylated polyethers such as DOW 190 and/or preservatives as specified in claims 5-6 and 16. There is no Response given at all to the arguments of nonobviousness presented with respect to the very specific and detailed method steps of claims 4-8 and 16. It is these steps which define the specific method which results in the unique multilamellar liquid crystal.

The underlying premise of all the rejections in this appeal is that claims in issue read on methods of formulating vesicles or liposomes. They do not. The present claims are directed at formulating a non-liposomal multilamellar liquid crystal carrier, by preparing a non-liposome multilamellar liquid crystal phosphatidylcholine non-polar carrier for topical administration; and mixing an insulin solution into the carrier to entrap the insulin within the carrier, wherein the insulin is stabilized at room temperature. The claimed “multilamellar liquid crystal carrier” is not a vesicle or liposome. It is not reasonable to interpret the claimed “multilamellar liquid crystal carrier” as a vesicle or liposome because a person of ordinary skill in the art would not interpret “multilamellar

liquid crystal carrier" as interpreted by the Examiner, and accordingly, the rejection should be reversed. *In re Buszard,* 504 F.3d 1364, 84 USPQ2d 1749, 1750-1751 (Fed. Cir. 2007).

Moreover, the Examiner's claim interpretation which reads "multilamellar liquid crystal carrier" on vesicles or liposomes is improper where, as in this case, the Applicant has affirmatively stated that "multilamellar liquid crystal carrier" does not encompass vesicles or liposomes. "When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art." *In re Zletz*, 893 F2d 319, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

In this case, the specification is explicit in saying what the invention is:

> "the PPC-enriched phosphatidylcholine forms a bilayer enveloping the polypeptide or macromolecule to create the topical drug delivery composition, contributing to the stability of the active molecule and enhancing penetration. Further, the topical drug delivery composition may be in liquid crystal phase, with the PPC-enriched phosphatidylcholine loosely arranged in multilamellar fashion, with the polypeptide or macromolecule being bonded and entrapped within the lipid bilayers formed therein, as disclosed in U.S. Patent Application No. 10/448,632 to Perricone. This forms a loosely arranged, yet stable, PPC-enriched phosphatidylcholine-drug complex that further increases penetration and delivery of the polypeptide or macromolecule to the dermal vasculature."

Specification at [0014]. Nowhere in the specification is the carrier described as a liposome.

If the Patent Office chooses to interpret "multilamellar liquid crystal carrier" as reading on liposome structures on the grounds that it is the "Broadest Reasonable Interpretation" standard, then not only is that an error because it is an unreasonably broad interpretation, but also because the standard itself is improper. See Bey & Cotropia, *The Unreasonableness of the Patent Office's "Broadest Reasonable Interpretation Standard*, 37 AIPLA Quarterly Journal 285 (Summer 2009). In particular, the "Broadest Reasonable Interpretation" standard is inconsistent with singular meaning of "invention" in Title 35, §§101-103, 112. If "multilamellar liquid crystal carrier" is interpreted to read on liposome structures applied, then the Patent Office procedure violates constitutional and legislative standards requiring consistency in the application of the patent laws.

This case involves the patentability of different crystal forms of the carrier. The present case is like many other cases where distinct polymorph forms of the same compound have been determined to be patentable, even where the polymorph had been previously produced. See e.g. *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995).

The claims of the present application are for method of formulating a multilamellar liquid crystal phosphatidylcholine and polyglycol mixture. The carrier composition is not a liposome, is a ***multilamellar liquid crystal***. The claimed crystal structure is obtained by the particular steps disclosed in the two examples in the Specification at ¶¶ [0017] – [0020]. A different series of steps would yield a different

crystal form, which would not be within the scope of the pending claims. Indeed, a comparison of the steps in the examples disclosed in the present application with the steps of the examples in the cited art reveals significantly different procedures, which necessarily result in different end products.

For the foregoing reasons, as well as those set forth in Appellant's previously filed Appeal Brief, Appellant respectfully submits that the claimed invention embodied in each of Claims 1-6, 8, and 11-16 is patentable over the cited prior art. As such, Appellant respectfully requests that the rejections of each of Claims 1-6, 8, and 11-16 be reversed.

Respectfully submitted,

/Stephen P. McNamara/

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